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Language improvement one week after thrombolysis in acute stroke

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Objectives – Language recovery following acute stroke is difficult to predict due to several evaluation factors and time constraints. We aimed to investigate the predictors of aphasia recovery and to identify the National Institute of Health and Stroke Scale (NIHSS) items that best reflect linguistic performance, 1 week after thrombolysis. *Materials and methods* – We retrieved data from a prospective registry of patients with aphasia secondary to left middle cerebral artery (MCA) stroke treated with intravenous thrombolysis. Complete recovery at day 7 (D7) was measured in a composite verbal score (CVS) (Σ Language+Questions+Commands NIHSS scores). Lesion size was categorized by the Alberta Stroke Program Early CT score (ASPECTS) and vascular patency by ultrasound. CVS was correlated with standardized aphasia testing if both were performed within a two-day interval. *Results* – Of 228 patients included (age average 67.32 years, 131 men), 72% presented some language improvement that was complete in 31%. Total recovery was predicted by ASPECTS (OR=1.65; 95% CI, 1.295–2.108; $P < 0.00$) and baseline aphasia severity (OR=0.439; 95% CI, 0.242–0.796; $P < 0.007$). CVS correlated better with standardized aphasia measures (aphasia quotient, severity, comprehension) than NIHSS_Language item. *Conclusions* – Lesion size and initial aphasia severity are the main predictors of aphasia recovery one week after thrombolysis. A NIHSS composite verbal score seems to capture the global linguistic performance better than the language item alone.

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Introduction

Aphasia is one of the most disabling neurological conditions, with a significant impact on quality of life, mood, and ability to return to work (1–3). It occurs in 15–40% of individuals with left hemisphere stroke and persists in 12.5–50% (3–6). Most data on aphasia recovery were obtained before the modern era of thrombolytic therapy. However, the treatment with recombinant tissue plasminogen activator (rTPA), particularly if early recanalization is achieved, can modify the size, pattern, and nature of infarcts following ischemic stroke (7–9). As a consequence, the linguistic impairments following a stroke as well as their expected prognosis could also be different. Given the current recommendation to use intravenous thrombolysis as the standard of care in acute stroke patients fulfilling the inclusion criteria, it is important to reevaluate the factors associated with aphasia recovery.

The outcome of aphasia is difficult to predict within the first days of stroke. Several reasons and time constraints preclude the use of standardized batteries of tests for language assessment before rTPA (5, 10). The NIHSS (National Institute of Health and Stroke Scale) is the gold standard assessment tool to evaluate neurological deficits in acute stroke patients. Nonetheless, the language item of the scale has been criticized due to its inability to differentiate between aphasic symptoms, its poor evaluation of comprehension, and its failure to identify mild symptoms (11, 12). A factor analysis of the NIHSS (13) identified two items that are loaded in the same factor as language: the request to answer some questions (item 1b) and the response to verbal commands (1c). Although not tackling language specifically, these items can be considered indirect measures of aphasia. In two recent studies (12, 14), they were used in a compound measure to evaluate language improvement, but so far they have not been validated as such.

In this study, we aimed to assess: (i) the validity of the NIHSS composite verbal score (CVS), comparing it to quantitative measures obtained in a standardized assessment; (ii) language recovery in the first week after thrombolysis and to identify prognostic factors among clinical and imaging variables.

Material and methods

Study design

Retrospective analysis based on a prospectively collected register of consecutive patients treated with intravenous thrombolysis for acute ischemic stroke. Data were collected in a Stroke Unit of a University Hospital according to a standard protocol between 2003 and 2014 and concerns two time points – on admission and on day seven (D7). The study protocol was approved by the joint Ethics Committee of the Faculty and Hospital.

Population

Records of consecutive patients with aphasia due to ischemic stroke of the left middle cerebral artery (MCA) territory admitted to a Stroke Unit for thrombolysis were selected. Aphasia was diagnosed by the attending neurologist, with experience in stroke based on a bedside language evaluation usually comprising spontaneous speech, naming and comprehension of commands. Any score ≥1 on the NIHSS Language item (item 9) was diagnostic of aphasia. All patients had two language evaluations, on admission (before thrombolysis) and on D7. Attending neurologists and residents have identical expertise in the NIHSS scale and participate in clinical trials that demand certification in the NIHSS scale. We excluded patients who did not complete the second evaluation due to death, unconsciousness, or transfer to other units, with the exception of those who were discharged before D7 without any language impairment, who were assigned a D7 language score of zero. Patients did not initiate Speech and Language Therapy before D7.

Aphasia severity was measured in a composite verbal score (CVS), ranging 0–7, corresponding to the sum of three NIHSS items: item 9 (NIHSS_best Language) with four possible degrees (0 = no aphasia or normal; 1 = mild to moderate aphasia; 2 = severe aphasia, and 3 = mute/global aphasia); item 1b (NIHSS_Questions), scoring 0, 1, or 2 (answers two questions correctly, one or none, respectively); and item 1c (NIHSS_Commands), scoring 0, 1, or 2 (performing both, one, or none correctly). Complete aphasia recovery was defined as a D7 CVS of zero. Aphasia improvement was defined as any decrease of one or more points in CVS between admission and D7.

Procedures

Demographic (age, gender, literacy) and clinical data were retrieved from the registry, including vascular risk factors, onset to needle time, baseline and D7 neurological status (total NIHSS score and verbal and right motor subscores), left internal carotid artery (ICA), and MCA patency verified by carotid and transcranial ultrasound, hemorrhagic transformation of the infarct, and modified Rankin scale at discharge.

All patients undertook an unenhanced brain CT scan before thrombolysis and received rTPA within the first 3 (between 2003 and 2010) or 4.5 h (2010–2014) of stroke onset. Subsequent brain imaging (CT or MRI) was performed in cases with no visible lesion in the acute CT, with suspected hemorrhagic transformation or other clinical reasons. Carotid Ultrasound and Transcranial Doppler were used to assess patency of the left MCA and ICA between 12 and 72 h.

Brain imaging analysis

Neuroimaging data were retrieved from medical records. Lesions were analyzed on the first CT or MRI performed after thrombolysis or on admission CT if there were no subsequent images. The analysis was performed by two independent examiners, blind to the clinical information, according to the Alberta Stroke Program Early CT Score (ASPECTS) (15) for the presence or absence of lesion in ten different areas of the left MCA territory. Affected regions are summed, and the total is subtracted from 10, producing a score ranging between 0 (lesion in all MCA territory) and 10 (no visible lesion). Every time there was no complete agreement, the images were reviewed and scored by consensus.

Standardized aphasia evaluation

Patients with persisting aphasia were also evaluated during admission by Speech and Language therapists using a standardized aphasia battery, the Lisbon Aphasia Assessment Battery (BAAL) (16), with tests of speech fluency, object naming, word and sentence repetition (producing a repetition score), object identification and comprehension of simple commands (producing a comprehension score) and two independent measures of aphasia severity: the Aphasia Severity Rating Scale (ASRS) of the Boston Diagnosis Aphasia Examination (17) and the aphasia quotient (AQ=the mean of correct percentage obtained in four BAAL subtests (fluency, naming, word repetition and comprehension of commands)). AQ is comparable its counterpart of the Western Aphasia Battery (18, 19).

Composite verbal score and the composing NIHSS scores at D7 were correlated with standard aphasia measures to evaluate their reliability. Assuming that aphasia severity suffers significant changes in the first days after stroke, correlations were calculated only for patients who undertook aphasia assessment between the day five and day nine (D7 ± 2).

Statistical analysis

Demographic, clinical, and imaging data were analyzed by descriptive statistics. Interrater reliability was evaluated by k statistics. Biserial point correlations were calculated between NIHSS scores and language tests scores. Patients were classified as recovered or not recovered (D7_CVS of 0 or ≥1, respectively), and the clinical and imaging features were compared between groups, by Student's *t*-test or Mann–Whitney *U*-test for continuous variables and chi-square for nonparametric variables. Factors considered relevant for recovery ($P \leq 0.15$ in univariate analysis) were entered in a multivariable logistic regression. Odd ratios and 95% CI were calculated.

The degree of CVS improvement was explored by linear regression analysis. As initial aphasia severity modulates the amount of possible recovery (more limited in low initial scores), improvement was calculated separately for mild aphasia (NIHSS_Language=1) and severe/global aphasia (NIHSS_Language >1) at baseline. Statistical analyses were performed using SPSS software package (SPSS version 21.0 for Windows, NY, USA). All statistical tests were two sided with significant levels at alpha <0.05.

Results

A total of 624 patients were admitted with aphasia due to acute MCA ischemic stroke, and 252 had undergone thrombolysis. Sixteen patients died, six were transferred to other units without a second evaluation, two were excluded because the lesion was on the right hemisphere, and 228 cases were included.

Patients were on average 68.3 years of age (range 25–87) and 57.5% were male patients. Mean CVS at entry was 5.15 with a median of 6 (range 1–7) (Table 1). Brain imaging was analyzed in 182 cases (79.8%), and 33 of these on MRI. In 46 earlier cases, imaging exams were not permanently stored. Cases without brain imaging did not differ from the others in demographics, risk factors, onset to needle time, baseline NIHSS (Total, best Language and CVS score), vessel patency, aphasia recovery, or improvement. Interrater agreement of ASPECTS score was 0.953 (Cohen Kappa, $P < 0.000$). The median value of ASPECTS was 7 (ASPECTS<7 in 86 (47.5%) patients). There was a negative but nonsignificant correlation between initial CVS and ASPECT score (Spearman's rho= −0.064, ns). The majority of patients had a single lesion of the left hemisphere but 24 presented previous vascular lesions, 16 on the right hemisphere. Hemorrhagic transformation occurred in 22.2%.

Aphasia recovery

By D7, 30.7% ($N = 70$) of patients had recovered completely and 71.9% ($N = 164$) presented some degree of improvement in the CVS. The majority (117) improved between 1 and 4 points, but 47 patients improved more than four points, including seven cases that improved seven points. Fifty cases remained unchanged and 14 worsened.

Differences between recovery groups are shown in Table 1. Patients who recovered had lower NIHSS_total, milder aphasia (CVS and NIHSS_best Language) and less right limb weakness (NIHSS score sum for right motor arm and leg) at baseline. In addition, they also had smaller infarcts and more often presented vessel patency and absence of hemorrhagic transformation.

A multivariate logistic regression analysis (Table 2) revealed that ASPECTS and baseline aphasia severity explained 45.7% of total recovery. The degree of CVS improvement (linear regression analysis) was related to ASPECTS, age, and initial aphasia severity, but the model was only significant for patients with a baseline NIHSS_best Language >1. Figure 1 shows the

Table 1 Comparisons between patients with or without total aphasia recovery

	Total	Complete recovery		P-value
		No	Yes	
N	228	158	70	
Age (sd)	68.32 ± 11.31	68.44 ± 11.89	68.03 ± 9.94	0.79
Literacy (sd)	6.04 ± 5.24	6.22 ± 5.27	2.00 ± 2.00	0.17
Gender (M:F)	131:97	91:67	40:30	0.95
Hypertension				
No	86	56	30	0.29
Yes	142	102	40	
Diabetes				
No	169	116	53	0.72
Yes	59	42	17	
Dyslipidemia				
No	153	104	49	0.54
Yes	75	54	21	
BL NIHSS_Total	15.23 ± 6.14	16.98 ± 5.61	11.27 ± 5.41	<0.001
BL NIHSS_Language				
1	38	13	25	<0.001
2	105	71	34	
3	85	74	11	
BL-CVS	5.15 ± 1.77	5.56 ± 1.62	4.24 ± 1.78	<0.001
BL Right Limb Weakness				
No	32	15	17	0.003
Yes	196	143	52	
Onset needle	150.6 ± 41.66	149.81 ± 45.67	152.37 ± 31.02	0.62
Vessel patency				
No	103	83	20	0.001
Yes	124	75	49	
ASPECTS Total	6.25 ± 2.70	5.37 ± 2.67	8.23 ± 1.41	<0.001
Single infarct				
No	24	18	6	0.43
Yes	158	108	50	
Previous Right hemisphere lesion				
No	166	115	51	0.002
Yes	16	11	5	
Hemorrhagic transformation				
No	144	92	52	<0.001
Yes	41	37	4	

Sd, standard deviation; M, male; F, female; BL, baseline; NIHSS, National Institute of Health and Stroke Scale; CVS, composite verbal score; ASPECTS, Alberta Stroke Program Early CT score.

pattern of improvement between baseline and D7 for each degree of initial aphasia and lesion size categorized as small (ASPECTS ≥7) or large (ASPECTS <7).

Reliability of NIHSS verbal scores

Thirty-four patients undertook a standardized aphasia evaluation between the day five and day nine coinciding with NIHSS 7D assessment ± 2 days. Correlations between the NIHSS scores and aphasia measures (Table 3) were significant and highest between the CVS and global measures of aphasia severity (AQ, BASR) or verbal comprehension. NIHSS_Commands had a higher correlation with comprehension measures than best Language or Questions items. And each NIHSS_Commands category corresponds to a different comprehension score in the standard Language Assessment, that ranges from 0 to 24 (score 0 = 20.2; score 1 = 14.4; score 2 = 7.3; ANOVA F = 8.62; $P = 0.001$).

The three items, composing CVS, presented an internal consistency of 0.723. There was a considerable overlap in the definition of total recovery in NIHSS_best Language and CVS on D7, yet two patients fully recovered according to NIHSS_best Language were considered impaired in CVS.

Discussion

In this study, we analyzed the outcome of acute aphasia seven days after thrombolysis for acute stroke. One-third of the patients recovered completely and another 40% presented some degree of language improvement. Lesion size (ASPECTS

Table 2 Multivariate regression analysis

				95% CI	
	Adjusted R^2	*P*	OR	Lower	Upper
Complete Aphasia recovery					
ASPECTS Score	0.457	0.000	1.652	1.295	2.108
Baseline NIHSS_Language		0.007	0.439	0.242	0.796
Vessel patency		0.049	0.432	0.187	0.998
Hemorrhagic transformation		0.156, ns	2.449	0.710	8.444
Baseline NIHSS_R Limb weakness		0.601, ns	1.305	0.482	3.531
Degree of CVS improvement (cases with baseline aphasia >1)					
ASPECTS Score	0.407	0.000	0.603	0.387	0.628
Vessel patency		0.074, ns	0.122	−0.055	1.160
Age		0.009	−0.170	−0.063	−0.009
Baseline NIHSS_Language		0.006	0.184	0.244	1.448
Baseline NIHSS_R limbs		0.345,ns	−0.065	−1.355	0.477

NIHSS, National Institute of Health and Stroke Scale; CVS, composite verbal score; ASPECTS, Alberta Stroke Program Early CT score; R, right; D7, 7th day post onset.

score) and baseline aphasia severity were the main predictors of total recovery. The degree of aphasia recovery between admission and D7 was inversely related to lesion size, age, and initial aphasia severity.

Each of the NIHSS items related to language (best Language, Commands, and Questions) presented significant correlation with standardized aphasia measures on D7, but their sum in a Composite Verbal Score correlated better with those measures. Those three items presented a good internal consistency between them, supporting previous studies showing that they are measuring identical functions (13). To note that NIHSS_Commands correlated better with language comprehension than NIHSS_best Language, thus adding another linguistic dimension to language assessment, not completely reflected in NIHSS_best Language. Despite being a rough measure with an insufficient number of items, NIHSS_Commands gives explicit information about auditory verbal comprehension. These results, together with the factor analytic structure of NIHSS (13), support the use of this composite score as an indicator of aphasia severity – although its validity as a diagnostic tool needs to be determined. This score can be particularly relevant for aphasia assessment given the widespread use of the NIHSS scale, allowing direct comparisons between different series of stroke patients.

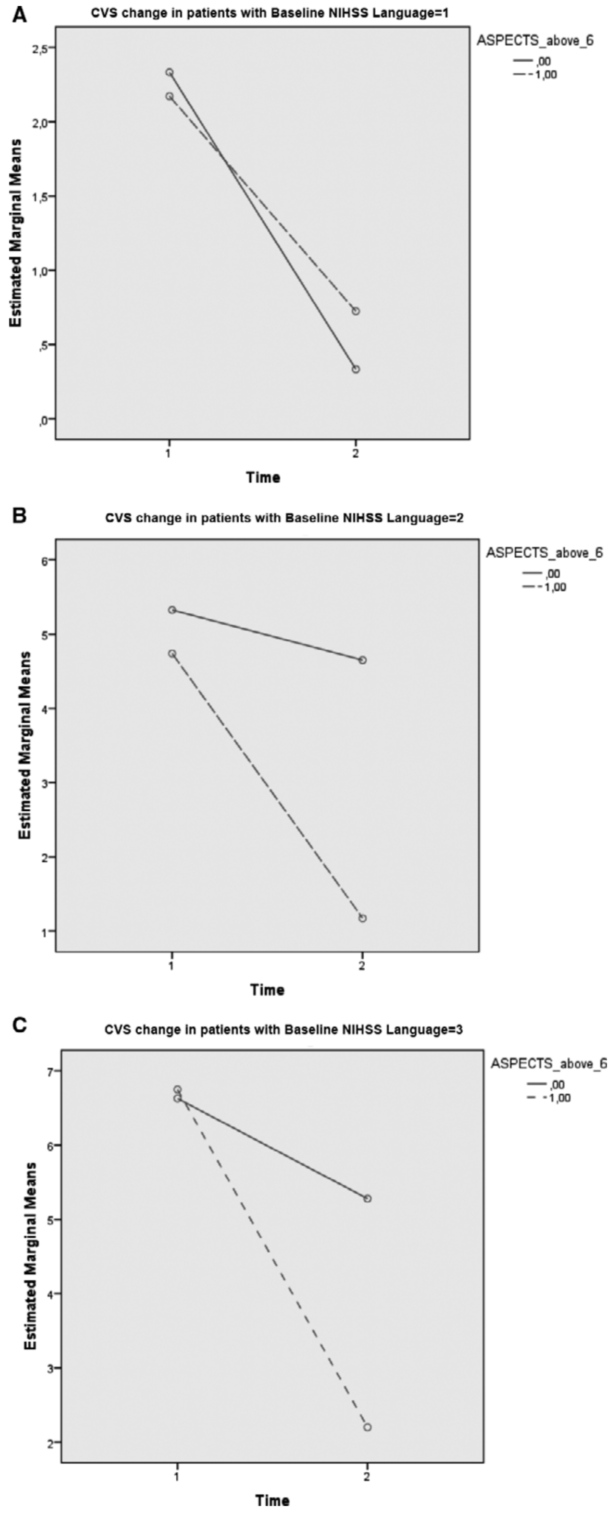

Figure 1. Composite verbal score improvement between admission (Time 1) and D7 (Time 2). Different lines correspond to lesion size in ASPECTS (bold line ASPECTS≥7; dotted line ASPECTS<7). Figures correspond to initial aphasia severity (NIHSS_Language score): A-mild aphasia; B-moderate/severe aphasia; C-global aphasia/mutism.

Table 3 Correlations between NIHSS language and composite verbal scores and standardized aphasia evaluation (N = 34)

	CVS	NIHSS Language	NIHSS Commands	NIHSS Questions
AQ	−0.544**	−0.388*	−0.496**	−0.428*
BASRS	−0.660**	−0.537**	−0.471**	−0.594**
Fluency	−0.453**	−0.415*	−0.144 (ns)	−0.539*
Naming	−0.409*	−0.268 (ns)	−0.431*	−0.258 (ns)
Comprehension Score	−0.583**	−0.450**	−0.609**	−0.342
Repetition Score	−0.369*	−0.242 (ns)	−0.217 (ns)	−0.400*

AQ, aphasia quotient; BASRS, Boston aphasia severity rating; CVS, composite verbal score; NIHSS, National Institute of Health and Stroke Scale.
**P-value<0.01
*P-value<0.05

Two previous studies with CVS (12, 14) including 129 left MCA cases and 100 cases with isolated aphasia, produced similar degrees of improvement, but did not take lesion size into account.

Language is a complex function, and improvement following stroke depends on different recovery and compensatory mechanisms deployed at different times. Functional reorganization is likely the main mechanism supporting language improvement in the subacute and chronic stages of aphasia (20, 21) – a process that can be enhanced by speech and language therapy as well as by other interventions acting on brain plasticity (22, 23). However, the mechanisms involved in acute recovery seem to be more related to the hemodynamic changes (24–26) that will determine the extension and nature of the ischemia or infarct, and possibly its distant effects on normal tissue. Thrombolysis contributes to this early recovery. Indeed, a retrospective observational study of two patient groups (those who received vs. those who did not receive thrombolysis) has shown that rtPA treatment improves the prognosis of aphasia at one week and three months after the stroke (27). Moreover, recanalization is associated with a decrease of several NIHSS scores at 24 h, including those composing the CVS (25). The contribution of recanalization/vessel patency to language improvement, in our study, also supports the role of hemodynamic mechanisms on the acute outcome. However, it is worth noticing that 49 cases had no vessel patency in the group of patients with complete recovery. The improvement observed in those cases may then be related to the collateral circulation, which restores perfusion with a reversion of initial diaschisis and ischemic penumbra.

Lesion size is particularly important in the acute and subacute stages (11, 13), suggesting that immediate language recovery depends more on intact areas of the left hemisphere than those of the right one. Indeed, the presence of previous areas of infarct in the right hemisphere did not modify the immediate outcome of aphasia in the present study. Lesion measurement is therefore important, and our semi-quantitative assessment of lesion size proved to be not only reliable, but also useful for the prognosis. However, it did not account for all variance in recovery or improvement. Among the variables not measured was diaschisis, a reversible metabolic depression observed in structurally unaffected areas of both cerebral hemispheres in the acute stage of stroke (28). Its reversibility may explain some degree of functional recovery. The poor correlation found on admission between aphasia severity (measured by the CVS) and the ASPECT score suggests that lesion alone does not account for aphasia severity and supports that diaschisis could play a role in the initial language impairment. On the other hand, patients with mild aphasia tend to have a good outcome independent of lesion size, which is usually small. In the present series, lesion size, among patients with mild aphasia (NIHSS_best Language = 1 at entry), was five in ASPECTS, and most cases (60%) scored between 7 and 9.

Although there was some association between the presence of limb motor impairment on admission and a worse outcome, the presence of limb motor deficits was not an independent predictor of aphasia recovery. Rather, aphasia and motor signs both reflect stroke severity.

We acknowledge limitations to the present study namely its retrospective design, the missing imaging data in some cases, the lack of compulsory MRI imaging that would give a better estimate of lesion size and number, the small subset of patients with standardized aphasia testing, and the lack of long-term follow up. Its strengths are the large series of patients included, the analysis of lesion size requiring only low technology as well as the use of a more comprehensive assessment tool.

The observation period of this study is long. However, the only change in patient management was the extension of the therapeutic window for thrombolysis from 3 to 4.5 h.

Although most patients with aphasia are expected to improve beyond the first week of stroke, the ability to predict aphasia recovery in the acute stage is valuable for patients, families, and clinicians. Families often seek reassurance about patient's recovery during their first encounter with the attending physician, who will have to estimate it from a limited number of measures. On the other hand, physicians need to anticipate the length of admission and rehabilitation needs. Hence, longitudinal studies are necessary to provide more definite answers about the outcome and to understand the role of endovascular therapy in acute aphasia recovery.

In conclusion, there is a tendency for an early recovery of aphasia during the first week after thrombolysis for acute stroke, which will be complete in about 30% of patients. A composite verbal score – which includes the NIHSS_best Language, Commands and Questions items – seems to capture better the overall linguistic performance of patients with aphasia than NIHSS_Language item alone. Lesion size, initial aphasia severity, and vessel patency are the main predictors of improvement.

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Conflict of interest

The authors report no conflict of interest.

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